Remarks

Amendments to the Claims

Claim 1 is amended to recite "a" periodontal disease.

Claims 35 and 36 have been amended to include periods at the ends of the sentences.

No new matter has been introduced as a result of the present amendments to the claims. Applicant reserves the right to pursue any subject matter canceled as a result of the present amendments in future prosecution, either in this application or in one or more continuing applications.

Claims Objections

Claim 16 is objected to because of the following informalities: The Examiner suggest that syntax of claim 16 can be improved by replacing the term "periodontal disease" with the term "a periodontal disease". Applicant has amended claim 1 by incorporating the Examiner's suggestion.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 35 and 36 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner notes that previously pending claims 35 and 36 lacked periods at the ends of the sentences. Claims 35 and 36 have been amended to include periods, rendering this rejection moot.

Rejections under 35 U.S.C. §102

Awaya et al.

Claims 16, 22-26, 36-42 and 48 have been rejected under 35 U.S.C. §102(b) as being anticipated by Awaya *et al.*, US patent 5,976,523 ("Awaya *et al.*"). Specifically, the Examiner asserts that Awaya *et al.* teaches a method for healing compromised tissues, including periodontal damage, comprising administering specific small molecule compounds in combination with additional substances, including GM-CSF. Applicant traverses this rejection.

Awaya *et al.* discloses methods and compositions for wound healing. To this end, Awaya *et al.* discloses synthetic pyrimidine compounds, either alone or in combination with other factors, for effecting such wound healing. Nowhere, however, does Awaya *et al.* disclose methods (or compositions) for the treatment of periodontal disease or for inducing tooth calcification, as recited in independent claims 16 and 37, respectively. Awaya *et al.* does disclose that their synthetic pyrimidine compounds can be used to treat "tooth extraction wounds" and "periodontal damage" (see col. 1, lines 21 and 12), both of which are characterized as types of wounds. The Examiner appears to have equated "periodontal damage" type wounds with the specific pathological condition of periodontal disease. Moreover, since claim 37 is rejected, the Examiner appears to imply that "tooth extraction wounds" can be treated by induction of tooth calcification, as recited in claim 37. Neither assumption is correct.

As described in the present application, periodontal disease is a pathological condition resulting from bacterial infection. See paragraph [0002] of the present application, published as US 2008/0038222A1, where it is described that "Periodontal diseases are caused by bacteria and toxins in dental plaque, which is a sticky colourless film constantly forming on the surfaces of the teeth." Paragraph [0021] summarizes embodiments that relate to the presently claimed methods, and is quoted below:

> According to one aspect the present invention relates to the use of at least one colony stimulating factor (CSF) or fragment or derivative thereof having essentially the biological functionality and activity of the CSF for preparing a medicament for the treatment of a localized bacterial infection and bacterial related disease, and calcification of affected bone tissue.

It is clear from these passages that a periodontal disease, as presently recited in claim 16, is not merely a wound that results in periodontal damage, as disclosed by Awaya *et al.*, but is in fact a specific pathological condition caused by bacteria. In short, periodontal damage is not the same as a periodontal disease. Awaya *et al.* does not disclose using the disclosed synthetic pyrimidine compounds, either alone in combination with other factors such as GM-CSF, to treat periodontal disease or any other condition caused by bacteria, and there is no evidence that such treatments were even considered. Indeed, a word search of the published Awaya *et al.* patent reveals that the term "bacteria" does not appear. The term "bacterial" appears only once in reference to a "bacterial colleganase" used to treat harvested rat cells after testing the effects of the synthetic

pyrimidine compounds on the enhancement of growth factors in a fulminant hepatitis disease model.

Regarding tooth calcification, a "tooth extraction wound" disclosed by Awaya *et al.* necessarily implies that the wound is caused by removal of a tooth. After removal, there would clearly be no tooth left on which to induce calcification. Thus, it is evident that induction of methods of inducing tooth calcification could not be used to treat a tooth extraction wound disclosed in Awaya *et al.*

Awaya *et al.* simply fail to disclose: 1) treatment of periodontal disease or any other condition caused by bacteria, or 2) induction of tooth calcification with any compound, including GM-CSF as recited in presently pending independent claims 16 and 37.

Moreover, Awaya *et al.* are completely silent regarding the feature recited in each of claims 16 and 37 that the GM-CSF polypeptide is locally administered by injection "in the proximity of the periodontal disease." As disclosed in paragraph [0029] of the present application:

> The present invention is based on the surprising discovery that **local administration** of a therapeutically effective amount of at least one CSF is susceptible of providing a substantial improvement of a **localized** bacterial infection and bacterial related disease. Indeed, as described in an example herein below, by injection of only one dose of a **GM-CSF** preparation into the gingival tissue in the **close vicinity of a tooth severely affected by periodontitis**, and in fact scheduled for removal, the tooth was saved: the dental status quickly improved without recurrence of the disease. (Emphasis added.)

It is black letter law that every recited feature must be considered in assessing novelty of the claimed methods.

In light of the present remarks, Applicant respectfully requests that the rejection of independent claims 16 and 37 under 35 U.S.C. §102(b) over Awaya *et al.* be withdrawn. Since each of claims 22-26, 36, 38-42 and 48 depends directly or indirectly from either claim 16 or 37, and thus incorporates the features recited claims 16 or 37, Applicant also requests that the rejection under 35 U.S.C. §102(b) of claims 22-26, 36, 38-42 and 48 be withdrawn.

Erickson-Miller et al.

Claims 16, 18, 22-26, 36, 37, 40-42 and 48 have been rejected under 35 U.S.C. §102(e) as being anticipated by Erickson-Miller *et al.*, US Patent Publication Number 2007-0105824 ("Erickson-Miller *et al.*"). Specifically, the Examiner asserts that Erickson-Miller *et al.* disclose a method of treating periodontal disease, gingivitis, tooth loss, and metastatic bone disease in a mammal by administering TPO receptor agonist in combination with another agent such as GM-CSF. Applicant traverses this rejection.

Erickson-Miller *et al.* is primarily directed to small molecule TPO receptor agonists for the treatment of various diseases. Such TPO receptor agonists are described as having certain stimulatory (e.g., anti-apoptotic) effects on a variety of cells. See, paragraph [0307] of Erickson-Miller *et al.*, where it is stated that:

> TPO is known to have various effects including anti-apototic [sic] survival effects on megakaryocytes, platelets and stem cells, and proliferative effects on stem cells and megakaryocytic cells (Kuter D. J. Seminars in Hematology, 2000, 37, 41-9). These **TPO activities effectively increase the number of stem and progenitor cells** so that there is **synergistic effects when TPO is used in conjunction with other cytokines that induce differentiation**.

There is no evidence in Erickson-Miller *et al.* that the TPO receptor agonists would have any effect on bacteria, i.e., the bacteria that cause periodontal disease.

In the very next paragraph (where GM-CSF is mentioned for the first time), Erickson-Miller *et al.* continue:

> The non-peptide TPO receptor agonists of the current invention are also useful in acting on cells for survival and/or proliferation in conjunction with **other agents known to act on cells for survival and/or proliferation**. Such other agents include but are not limited to: G-CSF, **GM-CSF**, TPO, M-CSF, EPO, Gro-beta, IL-11, SCF, FLT3 ligand, LIF, IL-3, IL-6, IL-1, Progenipoietin, NESP, SD-01, or IL-5 or a biologically active derivative of any of the aforementioned agents, KT6352 (Shiotsu Y. *et al.*, Exp. Hemat. 1998, 26, 1195-1201), uteroferrin (Laurenz J C., *et al.* Comp. Biochem. & Phys., Part A. Physiology., 1997, 116, 369-77), FK23 (Hasegawa T., *et al.* Int. J. Immunopharm., 1996, 18 103-112) and **other molecules identified as having anti-apoptotic, survival or proliferative properties for stem cells, progenitor cells, or other cells expressing TPO Receptors**. (Emphasis added.)

Thus, Erickson-Miller *et al.* disclose GM-CSF for use in combination with a TPO receptor agonist only because of its "anti-apoptotic, survival or proliferative properties" on cells.

As discussed above, however, periodontal disease is caused by a localized bacterial infection, and is not a result of apoptosis or non-proliferation of a subject's cells. See e.g., paragraphs [0002] and [0021] of the present application. Erickson-Miller *et al.* fail to disclose GM-CSF for the treatment of the bacterial component of periodontal disease. In fact, Erickson-Miller *et al.* fail to disclose any compound whatsoever, including their featured TPO receptor agonist compounds, for the specific treatment of a bacterial infection. A word search of the published Erickson-Miller *et al.* application reveals that the terms "bacteria" or "bacterial" (or any terms that stem from these base words) do not even appear in the application. As such, Erickson-Miller *et al.* fail to disclose compositions and methods for treating periodontal disease, as recited in currently pending claim 16.

Regarding claim 37, the Examiner also asserts that Erickson-Miller *et al.* teach a method of treating "tooth loss." Similar to the situation discussed above for Awaya *et al.*, "tooth loss" by its plain meaning necessarily indicates that the tooth is in fact "lost." After such loss, there would obviously be no tooth left on which to induce calcification. Thus, induction of tooth calcification could not be used to treat a tooth loss as disclosed in Erickson-Miller *et al.*

Moreover, like Awaya *et al.*, Erickson-Miller *et al.* are completely silent regarding the feature recited in each of claims 16 and 37 that the GM-CSF polypeptide is locally administered by injection "in the proximity of the periodontal disease." It is black letter law that every recited feature must be considered in assessing novelty of the claimed methods.

In light of the present remarks, Applicant respectfully requests that the rejection under 35 U.S.C. §102(b) over Erickson-Miller *et al.* be withdrawn. Since each of claims 18, 22-26, 36, 40-42 and 48 depends directly or indirectly from either claim 16 or 37, and thus incorporates the features recited claims 16 or 37, Applicant also requests that the rejection under 35 U.S.C. §102(b) of claims 22-26, 36, 38-42 and 48 be withdrawn.

Rejections under 35 U.S.C. §103

Claims 21, 32-35 and 43-47 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Awaya *et al.* in view of O'Uchi *et al.*, US Patent 6,682,718 ("O'Uchi *et al.*");

or Erickson-Miller *et al.* in view of O'Uchi *et al.* O'Uchi *et al.* is cited for disclosing features recited in each of claims 21, 32-35 and 43-47, namely injection through the mucosal lining of the gingiva or by application in a periodontal pocket, injection into the alveolar mucosa, injection into the sublingual mucosa, and injection into the palate part. The Examiner asserts that it would have been prima facie obvious to administer the compositions of Awaya *et al.* or Erickson-Miller *et al.* via such injection routes. Applicant traverses this rejection.

Awaya et al. in view of O'Uchi et al.

O'Uchi *et al.* disclose that **bisphosphonate acid derivatives** can be injected into various periodontal tissues to treat periodontal disease, which is disclosed to be a disease of bacterial origin. O'Uchi *et al.* disclose that the bisphosphonate acid derivatives can be injected through the mucosal lining of the gingiva or by application in a periodontal pocket, injection into the alveolar mucosa, injection into the sublingual mucosa, and injection into the palate part.

The Examiner asserts that it would have been obvious to combine the teachings of Awaya *et al.* with the teachings of O'Uchi *et al.* to arrive at the presently claimed methods. Applicant traverses this rejection, since one of ordinary skill in the art would have no reason to combine the teachings of the two references.

As discussed above, the synthetic pyrimidine compounds of Awaya *et al.*, and compositions comprising such compounds, are disclosed only for use in **wound healing**. There is no teaching or suggestion in Awaya *et al.* that the disclosed synthetic pyrimidine compounds can be used to treat bacterial-related diseases. Specifically, Awaya *et al.* neither teach nor suggest that their synthetic pyrimidine compounds (either alone or in combination with other components such as GM-CSF) can be used in the treatment of periodontal disease, or for inducing tooth calcification, as recited in independent claims 16 and 37, respectively.

One of ordinary skill in the art, upon reading Awaya *et al.*, would have no reason to suspect that the synthetic pyrimidine compounds, either alone or in combination with GM-CSF, would have any effect whatsoever on bacterial-related diseases, **regardless of whether such compounds are injected by the routes disclosed in O'Uchi *et al.*, or in fact any other route**. In light of the narrow teaching of Awaya *et al.*, one of ordinary skill in the art would have no motivation to apply its teachings to any of the variety of known bacterial-related diseases, and

would have no reason combine Awaya *et al.* with any reference that discloses treatment of such bacterial-related diseases (e.g., a periodontal disease).

In short, since one of ordinary skill in the art would have no reason to combine a reference that discloses synthetic pyrimidine compounds for use in wound healing (Awaya *et al.*) with a reference that teaches unclaimed compounds for the treatment of periodontal disease (O'Uchi *et al.*), it is improper to use the combination of such references in rejecting the presently pending claims.

Applicant respectfully requests withdrawal of the rejection of claims 21, 32-35 and 43-47 under 35 U.S.C. §103 based on the combination of Awaya *et al.* and O'Uchi *et al.*

Erickson-Miller et al. in view of O'Uchi et al.

The teachings of O'Uchi *et al.* are discussed above. The Examiner asserts that it would have been obvious to combine the teachings of Erickson-Miller *et al.* with the teachings of O'Uchi *et al.* to arrive at the presently claimed methods. Applicant traverses this rejection, since one of ordinary skill in the art would have no reason to combine the teachings of the two references.

As discussed above, the TPO receptor agonists of Erickson-Miller *et al.*, and compositions comprising such compounds, are disclosed as having certain stimulatory (e.g., anti-apoptotic) effects on a variety of cells. Erickson-Miller *et al.* disclose GM-CSF for use in combination with a TPO receptor agonist only because of its "anti-apoptotic, survival or proliferative properties" on cells. There is no teaching or suggestion in Erickson-Miller *et al.* that the disclosed synthetic TPO receptor agonists, either alone or in combination with GM-SCF, can be used to treat the bacterial component of a disease. Specifically, Erickson-Miller *et al.* neither teach nor suggest that their TPO receptor agonists (either alone or in combination with other components) can be used in the treatment of the bacterial component of periodontal disease, or for inducing tooth calcification, as recited in independent claims 16 and 37, respectively.

One of ordinary skill in the art, upon reading Ericson-Miller *et al.*, would have no reason to suspect that the TPO receptor agonists, either alone or in combination with GM-CSF, would have any effect whatsoever on the bacterial component of any disease, including periodontal

disease, **regardless of whether such compounds are injected by the routes disclosed in O'Uchi *et al.*, or in fact any other route**. In light of the narrow teaching of Erickson-Miller *et al.*, one of ordinary skill in the art would have no motivation to apply its teachings to any of the variety of known bacterial-related diseases, and would have no reason combine Erickson-Miller *et al.* with any reference that discloses treatment of such bacterial-related diseases (e.g., a periodontal disease).

In short, since one of ordinary skill in the art would have no reason to combine a reference that discloses TPO receptor agonists that have stimulatory effects on various cells (Erickson-Miller *et al.*) with a reference that teaches unclaimed compounds for the treatment of periodontal disease (O'Uchi *et al.*), it is improper to use the combination of such references in rejecting the presently pending claims.

Applicant respectfully requests withdrawal of the rejection of claims 21, 32-35 and 43-47 under 35 U.S.C. §103 based on the combination of Erickson-Miller *et al.* and O'Uchi *et al.*

Applicant has Discovered an Unknown and Unexpected Property of GM-CSF

As final matter, Applicant wishes to emphasize that he has discovered an entirely unexpected property of GM-CSF, namely that it is useful in the treatment of periodontal disease and in induction of tooth calcification when administered in the proximity of a periodontal disease. None of the references cited in this or in previous office actions would lead one of ordinary skill in the art to believe that GM-CSF has such a therapeutically beneficial property. To date, each of the several prior art rejections in the present case (many of which have already been successfully traversed) have strained to combine various portions of references having disparate, and sometimes contrary, teachings regarding periodontal disease, GM-CSF, and/or local administration methods. In making such rejections, the primary discovery of the present application that GM-CSF is useful in previously unrecognized clinical indications has been relegated to insignificance, or simply overlooked.

In contrast to all the references so far cited by the Examiner, Applicant has actually **reduced to practice** the claimed methods in a clinical setting. Example 1 shows that injection of GM-CSF in the proximity of the affected periodontal crevice resulted in a complete abolishment of periodontitis and re-attachment of the tooth to the jawbone. Similarly, Example 2 shows that

injection of GM-CSF in the proximity of the affected periodontal crevice in a different patient resulted in a complete abolishment of periodontitis.

Applicant strongly disagrees with the assertions made to date that such methods (and results) would have been anticipated or obvious, given that there is no evidence of record that anybody else has attempted (or even considered attempting) the claimed methods, much less achieved the beneficial results described in Examples 1 and 2. By demonstrating such beneficial effects in a clinical setting, Applicant has significantly expanded the available therapeutic options for the treatment of periodontal disease and for inducing tooth calcification. Applicant respectfully requests that the Examiner consider the significance of such a medical advance when assessing patentability of the presently pending claims.

Conclusion

In light of the present remarks, Applicant submits that the present application is in condition for allowance, and respectfully requests a notice to that effect. If the Examiner feels that it would further prosecution or expedite allowance of the present case, he is invited to telephone the undersigned at 612-766-2071.

Please charge the any required fees or other charges, and credit any overpayments, to deposit account 06-1050, referencing Attorney Docket No. 15665-0010US1.

Respectfully submitted,

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